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09/295,663	04/21/99	JOSHI	P 16303-007120

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/295,663	Joshi et al.
Examiner	**Group Art Unit**
Joseph Woitach	1632

☒ Responsive to communication(s) filed on *Jan 11, 2001*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *38-44 and 46-77* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *38-44 and 46-77* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

File

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph Woitach** and the group art unit is now **1632**.

This application is an original application filed April 21, 1999, and claims benefit to provisional applications 60/082,665, filed April 22, 1998, 60/111,635, filed December 9, 1998, and 60/111,637, filed December 9, 1998.

Applicants amendment filed January 11, 2001, paper number 9, has been received and entered. Claims 1-37 and 45 have been canceled. Claims 38 and 55 have been amended. Claims 56-77 have been added Claims 38-44 and 46-77 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-44, 46-55 stand rejected and claims 56-77 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of cancer cells in a subject, the method comprising administering an amount of vincristine sulfate and cisplatin in an amount effective to inhibit growth of said cells at or

around the site of the tumor, and administering to said cells a polynucleotide encoding a gene which is well known in the art to inhibit cell growth, does not reasonably provide enablement for a method of enhancing the therapeutic effect of a foreign gene administered to a patient.

Applicants argue that undue experimentation is not necessary to practice the claimed invention citing *Ex parte Forman* and *In re Wands*. Further, Applicants argue even if experimentation is complex or extensive, does not mean that the invention is not enabled. Specifically, Applicants argue enablement in light of 1. the animal models provided, 2. administration of the gene delivery vehicle, 3. targeting of the DNA vehicle, and 4. gene transfer efficiency. Applicant arguments have been fully considered but not found persuasive.

Relevance of animal models.

Applicants argue the relevance of animal models in studying cancer pointing to Roth *et al.* as an enabling disclosure, and Applicants own example of expression of IL-12 and the combination of HSV-TK and ganciclovir. Examiner agrees with Applicant and the Orkin reference of the value of animal models serve as models, however as indicated in the previous office action Orkin points out the limitations of animal models, in particular that animal models are less predictive when applied to cancer. Applicants invention encompasses the treatment of any type of cancer in a patient and argue that it would be routine experimentation to practice the claimed method, however the art recognizes that the available animals models do not adequately represent working models. Therefore, for the routine experimentation to develop proper dosages and means of administration, the correct animal models should exist, however the present

specification does not provide any guidance on how to create the numerous breadth of models needed to practice the invention as claimed. Applicants working examples represent only well known working examples in the art, as presented in the USC 102 and USC 103 rejections below. Applicants cite *In re Jolles* for support of animal models for evidence of human utility, and point out that Crystal clearly accepts animal models (Applicants amendment page 7). Again, Examiner does not contend that animal models are not useful, or that Applicants examples do not provide sufficient utility, instead, it is maintained that the present disclosure does not provide adequate guidance on all the necessary animal models to make and use the invention in the breadth as claimed. Further, with respect to new claims, claim 69 and dependent claims are not directed to treatment of specifically cancer cells and encompasses any therapeutic effect for any complication a patient with cancer might have, and claim 74 and dependent claims encompass clearly is directed to any therapeutic effect. As pointed out in the previous office action, the art recognizes the art of gene therapy is unpredictable, and the present application fails to provide a nexus between the art recognized limitations known in the art and the means of routine experimentation to practice the claimed method for all types of cancer and with respect to new claims any possible therapeutic effect a patient may have.

Administration of the gene delivery vehicle and Targeting of the DNA vehicle.

Applicants argue that Bischoff *et al.* provides guidance for intratumoral administration, and that the present application provides recitation of several routes of administration, and that the FDA has approved over 200 clinical trials. Examiner does not contend certain modes of

delivery are not enabled for delivery of polynucleotide to a cell instead, that the present specification does not provide adequate guidance for one of ordinary skill in the art to practice the invention as claimed in the full breadth. As noted above, with respect to new claims, claim 69 and dependent claims are not directed to treatment of specifically cancer cells and encompasses any therapeutic effect for any complication a patient with cancer might have, and claim 74 and dependent claims encompass clearly is directed to any therapeutic effect. In addition to any delivery vehicle by any route, the breadth of the claims now encompass any form of gene therapy. As reasoned above, the art recognizes the art of gene therapy is unpredictable, and the present application fails to provide a nexus between the art recognized limitations known in the art and the means of routine experimentation to practice the claimed method for all types of cancer and with respect to new claims any possible therapeutic effect a patient may have. Further, the specification is silent with the necessary guidance for the use of specific genes for specific diseases. Finally, with respect to delivery, the claims encompass cell specific delivery by any route to any part of the patient. New claims 71-73 recite that the agent and therapeutic gene are administered distally from the tumor either IV or IP. Applicants argue that Dachs *et al.*, Deonarian, Miller *et al.* and the present specification provides guidance and working examples of targeted gene delivery. Beyond the complications of targeting tissues like the brain, which contain physical barriers to delivery of many compounds, the specification fails to provide the means to target a vehicle to a specific target cell. The specification teaches only a liposome composition without the details of how to target a particular cell of interest. The mere recitation

of various delivery vehicles does not provide adequate guidance for one of ordinary skill in the art to practice the invention. As pointed out in the cited references of record, the art recognizes the limitations of gene delivery and so because the present specification relies on the teachings of others for delivery, also is presented with the same limitations. From the specification, it is unclear how a the composition can be used for IP or IV injection for the tissue specific delivery of a liposome to the brain or any specific tissue for that matter, since the liposome will circulate freely and most likely be cleared by the liver. The present specification fails to provide the necessary guidance needed to obtain the tissue specific delivery, or the necessary guidance for choosing the correct gene under the proper promoter for a therapeutic effect to treat cancer or any other disease encompassed by the claims. The reliance of the teachings of others and examples which reflect art recognized models present in the specification fails to provide the nexus and necessary guidance to overcome the art recognized limitations of gene therapy.

Gene transfer efficiency.

Applicants argue that contrary too Examiner's statements, that Crystal teach that gene therapy is a viable method to treat patents and that Crystal describes the prospects of gene therapy as a whole as an impressive accomplishment. Examiner agrees as a whole, the cited references of Crystal, Orkin and Motulsky, Verma and Soia, each support the ability to deliver a specific nucleic acid to an organism and yield a effect, however, however each references point out that there has been limited success in the field of gene therapy, and the authors point out that the art recognizes that there are many limitations that still exist which limit the ability to routinely

practice the methods gene therapy. As succinctly summarized by Verma and Somia "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." As discussed in detail in the previous office action, there are several art recognized limitations and unpredictability issues regarding gene therapy, that include: vector to be used for gene expression, production of effective concentration of the candidate protein, delivery of the protein or gene to target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the protein *in vivo*. Applicants specification relies in great part on the methods known in the art to practice the full scope of their invention and thus, are subject to the same limitations presently recognized in the art. For example, Examiner notes that the specification discloses different viral vectors-adeno-, adeno-associated and retro-viral vectors used for gene therapy, however, as previously discussed above all these vector systems have limitations and the specification does not provide any guidance as to how an artisan would have addressed these limitations. The claimed invention requires the delivery of a polynucleotide to any cell in any organism as an essential element to practice claimed method, however the specification fails to provide a nexus between these many art recognized shortcomings of gene delivery to an organism and the practice of the full scope of the claimed invention.

Applicants argue that in view of the art and, most importantly, the specification teachings, the claimed invention is predictable. Examiner strongly disagrees and in view of the silence of the present specification teachings and examples of how their methods differ from those presently

found in the art, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression which would result in a desired effect. Applicants argue that the amount of experimentation is routine by a person of ordinary skill in the art. As noted by Applicants, the invention is not directed to a new method, nor specific vector for transforming cells, nor to a particular heat inducible promoter, nor a particular gene of interest, nor a particular host cell, and Examiner agrees that practice of the claimed method *in vitro* may require routine experimentation *in vitro*, however the claims encompass the practice of the method *in vivo*, and as such requires the presence and/or delivery of the a polynucleotide to any cancer cell within a subject, and new claims encompass the delivery to any cell for any desired therapeutic effect. Applicants have described a method for a potential strategy to obtain increased therapeutic effect of a gene of interest however essentially all of the work required to ultimately develop the methods has been left for others. In the instant case, the specification is not enabling for the claimed invention because the arts of gene therapy are highly unpredictable as recognized in the prior art and because the specification as filed does not provide sufficient guidance, evidence and exemplification as to how an artisan would have carried out the claimed methods of controlling expression in any cell or organism, methods of therapy and would have addressed unpredictability issues as raised above, without undue experimentation.

Therefore, for the reasons above and of record, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the

claimed invention, it would have required one of skill in the art undue experimentation to practice the invention as claimed, and the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-44 and 46-55 stands and 56-77 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 38-44 and 46-55 and newly added claims 56-77 are unclear in the recitation of 'cell cycle blocker.' Applicants argue a 'cell cycle blocker' is adequately defined in the specification pointing to page 13, lines 4-10 and state that a 'cell cycle synchronizer' and 'cell cycle blocker' can be used interchangeably and would have been entirely clear to one of skill in the art (Applicants amendment page 13). Applicants arguments have been fully considered but not found persuasive. Examiner disagrees because the art recognizes a cell cycle synchronizer as an agent which coordinates a composition of cells into the same growth phase, however, Applicants have pointed to various examples of compounds known to be DNA damaging agents, and do not necessarily synchronize nor block the cell cycle but only damage the DNA. Often after administration the cell cycle is slowed down during DNA repair, but the cells are not necessarily synchronized nor blocked. Further, after administration of large enough amounts of many of the

compounds disclosed in the present specification, damage to the DNA in the cells results in cell death or complete arrest in the cell cycle and it is not clear from the specification if this would be considered a block since the damage is permanent and can not be restored as recognized by one of ordinary skill in art. Therefore, for the reasons above and of record the rejection is maintained.

Claims 55 and 56 are unclear because the method steps do not clearly relate to the preamble and clearly define what a 'foreign therapeutic gene' has to do with enhancing the therapeutic effect of a cell cycle blocker. Further, though administration is to a patient having cancer, it is unclear if the therapeutic effect is directed to the cancer in the patient or to elicit some other therapeutic effect

Claim 57 is unclear because 'said first stage of the cell cycle' has no antecedent basis in claim 38. Further, it is unclear to what the first stage of the cell cycle refers since the art does not recognize any particular phase as the first phase, only G1, S, G2, M (and the various specific phases of mitosis) and Go.

Claim 58 is unclear because there is no correlation with the first phase and the break down of the nuclear membrane as recited in claim 57.

Claim 59 is unclear on the recitation of 'at late S phase' because the exact time of this period is not clearly defined in the specification. Late S phase is indefinite and it would be unclear to one of ordinary skill in the art to the metes and bounds encompassed by late S phase without other specific and distinguishing features defined to specifically define what is meant.

Claim 61 is unclear and confusing because how or what is meant by the nucleic acid accumulating, and how this relates to the limitation of a phase other than the M phase is not clearly defined.

Claim 65 is unclear because there is no antecedent basis for 'said first stage' nor 'said second stage' in claim 38.

Claims 66 and 67 are unclear in the recitation of 'toxic to the cell' when read in light of the specification Applicants examples of pro-drug converting enzymes, such as HSV-TK, however they do not provide examples of genes which are directly toxic to the cell. Further, it is unclear how something that is toxic and cause apoptosis can be therapeutic to the cell since it kills the cell.

Claim 68 is unclear because it does not seem to further limit claim 38, and in fact may increase the breadth of the claim since any lipid formulation may be implied.

Claim 69 is unclear because while the claim recites a patient having cancer, the administration of a therapeutic gene is not limited of treatment of cancer. It is unclear if the enhanced therapeutic effect is for any gene of interest for any disease or complication a person with cancer might have.

Claim 70 is unclear because 'said cancer' has no antecedent basis in claim 69.

Claim 74 is unclear in light of the present specification since claim 74 clearly encompasses any therapeutic effect, however the present specification primarily teaches treatment of cancer

cells. It is unclear how the described method would be useful or applied to non-cycling cells in a patient.

Claim 77 is vague and unclear because how one would calculate the amount of lipid is unclear. It is not clear what is being compared or to what the calculation is in reference, the polynucleotide, the Gm1, the agent, recited in claim 74. Further, it is not clear if it is 1%-20% by weight, by volume or by some other reference.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38-44, 46, 47, 49, 52 and 55 stand and claims 56-73 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Roth *et al.*

It is noted that claim 38 and 55 has been amended to recited a lipid formulation which is resistant to DNAse treatment, and that new claims 56-73 are not restricted to this limitation. Applicants argue that Roth *et al.* do not teach the new limitation recited in claims 38 and 55, and further, with respect to new claims 56 and 69, that Roth *et al.* do not teach systemic administration. Applicants arguments have been fully considered but not found persuasive.

Examiner agrees that Roth *et al.* do not specifically recite that the lipid compositions taught are resistant to DNAse treatment, however Roth *et al.* teach many of the same lipid formulations taught in the present specification, and provide similar guidance for the administration of the lipid-DNA complex. Therefore, in the absence of evidence to the contrary, since the formulations are similar in both specifications it would be considered by one of ordinary skill in the art that both of the lipid formulations in both specifications would inherently meet this limitation. In addition, it is noted that new claims do not encompass this limitation. With respect to the systemic delivery, Examiner would point out this delivery taught and the various methods of administration are specifically claimed in claims 38 and 88. Therefore, for the reasons above and of record the rejection is maintained.

Claims 38-44, 46, 4, 49, 52 and 55 stand and claims 56-73 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Son *et al.*

Applicants argue that Son *et al.* do not teach a therapeutic gene. Further, Applicants argue that Son *et al.* do not teach specifically that the claimed liposome-polynucleotide compositions are resistant to DNAse treatment. Applicants arguments have been fully considered but not found persuasive. Examiner agrees with Applicant that Son *et al.* do not disclose a specific therapeutic gene, however they do teach that the methods described therein are for use in gene therapy, in particular for the treatment of tumors (page 12672; first column). As in the present specification, the use of a reporter gene provides the working model and preliminary

guidance for administration, and the specific gene to be used would depend on the specific knowledge of the type of cancer or tumor being treated. Given the general guidance of both Son *et al.* and the present specification, one of ordinary skill in the art would anticipate the invention as claimed. In addition, as reasoned in the preceding rejection above, Examiner agrees that Son *et al.* do not specifically recite that the lipid compositions taught are resistant to DNAse treatment (it is noted that new claims do not encompass this limitation), however Son *et al.* teach the same lipid formulations taught in the present specification, and provide similar guidance for the administration of the lipid-DNA complex. Therefore, in the absence of evidence to the contrary, since the formulations are similar in both specifications it would be considered by one of ordinary skill in the art that both of the lipid formulations in both specifications would inherently meet this limitation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 53 and 54 stand and claims 55-73 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.* and Son *et al.*

Applicants argue to establish a *prima facie* case that there must be adequate motivation or suggestion to combine the references, a teaching that there is a reasonable expectation of success, and that the combined references must teach all the elements of the claimed invention. Specifically, Applicants argue that there is no motivation to combine Roth *et al.* and Son *et al.*, nor is there a reasonable expectation of success given each of the separate references. Further, Applicants traverse Examiner's assertion that one of ordinary skill in the art would know how to create liposome-polynucleotide compositions which are resistant to a DNAse treatment as recited in the amended claims. Applicants arguments have been fully considered but not found persuasive. As reasoned in the preceding rejections above, Examiner agrees that Roth *et al.* and Son *et al.* do not specifically recite that the lipid compositions taught are resistant to DNAse treatment (it is noted that new claims do not encompass this limitation), however Roth *et al.* and Son *et al.* teach the same lipid formulations taught in the present specification, and provide similar guidance for the administration of the lipid-DNA complex. Applicants traversal is confusing since the present specification reviews the teaching in the art and summarizes the optimization needed to obtain liposome formulations for *in vivo* delivery and cites US Patent 5,705,385, issued January 6, 1998, (which is before the submission of the provisional applications). It is clear from the summary of the present specification and cited references that Applicants appreciated the teachings in the art. Therefore, in the absence of evidence to the contrary, since the formulations are similar in both specifications it would be considered by one of ordinary skill in the art that both of the lipid formulations in both specifications would inherently meet this limitation.

Applicants do not specifically point out why one would not be motivated to combine the references nor why there would not be an expectation of success. Clearly, each reference contains teachings for the treatment of tumors, in particular, specific methods for the delivery of DNA damaging agents for the increased transfer of liposome-polynucleotide compositions for an increased therapeutic effect. Each provide working examples and provide adequate guidance in the method sections for one of ordinary skill in the art to reproduce the teachings.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 38 and 48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Son *et al.* Roth *et al.* and Walker *et al.*

Applicants argue that Son *et al.* and Roth *et al.* do not teach all the necessary elements to anticipate the claims, and that Walker *et al.* does not remedy the deficiency. Applicants arguments have been fully considered but not found persuasive.

As noted above, Roth *et al.* and Son *et al.* do not specifically recite that the lipid compositions taught are resistant to DNAse treatment, however Roth *et al.* and Son *et al.* teach the same lipid formulations taught in the present specification, and provide similar guidance for the administration of the lipid-DNA complex which anticipates claim 38. Walker *et al.* was introduced to teach the limitation that the liposome contain a secondary agent, in this case a 'cell cycle blocking agent'. As is know in the art and noted in Roth *et al.* and Son *et al.* liposomes are

known vehicles for the delivery of polynucleotides. In addition, it is well known in the art that other compounds can and are delivered by means of a liposome carrier, and Walker *et al.* was introduced to provide an example of this teaching. Specifically, Walker *et al.* disclose the systemic delivery of agents by means of a liposome. If the delivery of the cell cycle blocking agent and polynucleotide were to be delivered at the same time, one of ordinary skill in the art would be motivated to combine the nucleic acid and agent in one liposome for a single delivery vehicle. In addition, the agent and polynucleotide delivered can be administered in specific combinations to for optimization of concentrations of both agent and polynucleotide. Applicants do not specifically point out why one would not be motivated to combine the references nor why there would not be an expectation of success. Clearly, each reference contains teachings for the delivery of liposomes for treatment, and though Roth *et al.* does not provide a specific example, the specification does teach that 'the DNA damaging agent may be prepared and used in combined therapeutic compositions, or kit, by combining it with a p53 protein, gene or gene delivery system' clearly indicating that Roth *et al.* appreciated that various combinations of polynucleotides and agents could be combined for more effective treatment. Each reference provides the motivation of utilizing liposome in combination with a polynucleotide or an agent. Each provide working examples and provide adequate guidance in the method sections for one of ordinary skill in the art to reproduce the teachings.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 74-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.* and Son *et al.* as applied to claims 38, 53-73 above, and further in view of Bally *et al.* (US Patent 5,705,385).

Claims 74-77 encompass a method for enhancing the therapeutic effect of a foreign gene administered to a patient comprising: administering a cell cycle blocker to a patient, and administering a therapeutic gene wherein the gene is in a lipid formulation consisting of PEG-lipid derivative (PEG-ceramide-C14, -C20 and -C8)and a Gm1-modified lipid.

Roth *et al.* and Son *et al.* are summarized above. Briefly, Roth *et al.* and Son *et al.* teach a method of enhancing the therapeutic effect of a foreign gene comprising administering a DNA damaging agent to the cell to inhibit the cell cycle and administering a foreign gene (encoding p53 and IL-12) to a patient. Roth *et al.* and Son *et al.* teach various liposome compositions however they do not teach the lipid composition comprising a PEG-lipid derivative and a Gm1-modified lipid. Bally *et al.* teach lipid-nucleic acid particles for the delivery and use in gene transfer, in particular the use of PEG-lipid derivative and a Gm1-modified lipids to prevent particle aggregation (columns 12-13; bridging paragraph). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the system described by Bally *et al.* with the specific vectors taught by Roth *et al.* and Son *et al.* to create the lipid-polynucleotide compositions for delivery of a gene. One having ordinary skill in the art would have been motivated to use the lipid compositions taught by Bally *et al.* for optimization of delivery and to prevent the aggregation of particles. (Bally, column 13; lines 1-7).

There would have been a reasonable expectation of success given the results of Roth *et al.* and Son *et al.* to deliver a polynucleotide with the liposomes specifically disclosed therein, and substitute the various lipid compositions taught by Bally *et al.* to optimize delivery of the polynucleotide to a particular cell type to reproduce the disclosed method of enhancing delivery and therapeutic effect of the gene.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER